



Health Protection Research
Unit in Emerging and Zoonotic
Infections at University of Liverpool

International Conference on Lyme Borreliosis and other Tick-borne diseases (ICLB)

4th – 7th September
Royal Tropical Institute (KIT)
Amsterdam, The Netherlands.





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LYME ARTHRITIS

AN EPIDEMIC OF OLIGOARTICULAR ARTHRITIS IN CHILDREN
AND ADULTS IN THREE CONNECTICUT COMMUNITIES

ALLEN C. STEERE, STEPHEN E. MALAWISTA, DAVID R. SNYDMAN, ROBERT E. SHOPE,
WARREN A. ANDIMAN, MARTIN R. ROSS, and FRANCIS M. STEELE





An epidemic form of arthritis has been occurring in eastern Connecticut at least since 1972, with the peak incidence of new cases in the summer and early fall. The illness swells...



Lyme Disease—A Tick-Borne Spirochetosis?
Author(s): Willy Burgdorfer, Alan G. Barbour, Stanley F. Hayes, Jorge L. Benach, Edgar Grunwaldt and Jeffrey P. Davis
Source: *Science*, Jun. 18, 1982, New Series, Vol. 216, No. 4552 (Jun. 18, 1982), pp. 1317-1319
Published by: American Association for the Advancement of Science



Ötzi - Ötztal Alps
3350-3105 BC

Old Lyme –
arthritis
Published 1977

Borrelia
burgdorferi
Published 1982

Where are we
now? ICLB 2022
research
update?

Sunday 4th September: Opening Session

Keynote speakers:

Linden Hu (Tufts University, USA): 'Pressing issues & major breakthroughs in Lyme disease'

Jaap van Dissel (RIVM, The Netherlands): 'What's ticking between science, patients and politics'

Keynotes were a nice summary to frame the talks that were scheduled over the conference

Linden Hu referenced the difficulties in the Lyme disease research landscape

- Lyme testing: diverse biobanks/simplified approvals process/improved collaborations
- Prevention methods can be difficult/concerns about vaccine hesitancy
- No treatment for chronic Lyme/Post-treatment LD syndrome
- Differences within groups of patients studied
- Understanding the disease process

While **Jaap van Dissel** spoke about what can be learned from interactions between policy makers, patients and scientists/clinicians to improve patient trust

Monday 5th September Session: 'New and Hot'

Only the highlighted talks were discussed

- **John Branda (Invited speaker – Harvard University, USA): 'What's new in Lyme diagnostics?'**
- **Daniel Ruzek (Invited speaker – Czech Academy of Sciences, Czech Republic) 'New directions of therapy of tick-borne encephalitis'**
- **Nerina Jusofovic (University of Kentucky, USA) 'Borrelia burgdorferi PlzA is a c-di-GMP dependent DNA binding protein'**

Basic science: Future translational potential as a unique protein important for zoonotic cycle and infectivity

- **Allen Steere (Invited speaker, Harvard Medical School, USA) 'Autoimmunity to synovial fibroblast-derived extracellular matrix proteins in patients with post-infectious Lyme arthritis'**

John Branda - 'What's new in Lyme diagnostics?'

- Summary of useful methodology and where things are moving
- Unmet needs: early sensitivity/active vs past infection/antibody info/predictors of PTLDS
- Rapid/point of care testing
- Indirect and direct testing methodology
- Multiplexed serological assays (quantitative/adaptable)
- Cellular assays (cautionary tale for Europe later though!)
- Use of Omics – disease signatures (urine and serum)
- Restricted by how we validate new methods: heterogeneity/mimicking conditions/control groups
- Often we are looking at validating in EM patients and healthy controls

Allen Steere: Post-infectious Lyme arthritis research has led to a three part hypothesis for mechanism:

- Joint collagen infected with strains of Bb causing inflammation
- Increased inflammatory response with an increase in antigen presenting molecules at the cell surface
- Molecular mimicry (borrelia and collagen) lead to T-cells reacting against collagen

He hasn't ruled out that there may be fragments of Bb left after treatment

We really need to be able to understand who will be at risk early in infection to be able to appropriately dampen the immune response.

Monday 5th September

Session: Epidemiology

Only the highlighted talks were discussed

- **Kees van den Wijngaard (Invited speaker, RVM, The Netherlands) 'why are we so bothered about ticks? Or the surveillance pyramid of European Lyme borreliosis from a Dutch perspective'**
- Christine Hagermann, (Pfizer, Germany) 'Epidemiology and costs of Lyme Borreliosis in Germany – A retrospective claims data analysis'
- **Alison Hinckley (U.S. CDC) 'Utility of commercial insurance claims to define the incidence of Lyme disease during pregnancy'**

Epidemiology session talks on understanding public response in relation to actual risk (Dutch study) and use of insurance claims data to understand costs of Lyme disease (Germany) and to look at LB in pregnancy.

Monday 5th September

Poster pitches: 3 minute presentations on selected posters:

Only the highlighted poster was discussed

- Duration of symptoms among clinician-diagnosed Lyme disease patients in the Northeast and Upper Midwest, United States
Sara Niesobecki, United States (Connecticut Emerging Infections Program/Yale School Of Public Health)
- Persistent *Borrelia burgdorferi sensu lato* infection after antibiotic treatment: a systematic overview and appraisal of the current evidence from experimental animal models
Amber Vrijlandt, Netherlands (Amsterdam University Medical Centers)
- Transcriptome mapping of *B. burgdorferi* reveals RNA regulators
Philip Adams, United States (National Institutes of Health)
- Investigating small and medium-sized mammals to identify potential reservoirs of *Borrelia miyamotoi* in the North Central U.S.A. Seungeun Han, Sweden (National Veterinary Institute)
- **Development of a multiplex peptide ELISA for serological identification of *Borrelia burgdorferi sensu stricto*, *B. garinii* and *B. afzelii* in human sera**
Antonio Foddai, United Kingdom (University Of Aberdeen)
- Designing a cocktail vaccine against Lyme borreliosis combining tick- and *Borrelia*-derived antigens
Alexis Burnham, Netherlands (Amsterdam University Medical Center)

Monday 5th September

Session: Clinical aspects: Introduced by Franc Strle (Slovenia)

Only the highlighted talks were discussed

- **Gary Wormser (Invited speaker, New York Medical College, USA). 'Lyme disease; from acute disease to persisting symptoms'**
- **Sergio Hernández (New York State Dept of Health, USA) 'Unique Clinical, Immune and Genetic signatures in patients with Borrelial Meningoradiculoneuritis'**
- Marika Nordberg (Åland Central Hospital, Finland) 'Tick-borne encephalitis in the Åland islands 2006-2020: Incidence and clinical characteristics since implementation of mass vaccination

Interesting talk on TBE that may be relevant to the UK in years to come: Incidence has not changed since vaccination program introduced. Many cases are incompletely vaccinated or have not had any vaccinations

- **Daša Stupica (UMC Ljubjana, Slovenia) 'Treatment of EM with Doxycycline for 7 days versus 14 days: A noninferiority randomized open-label study'**

Gary Wormser presented a pre-recorded talk and discussed prophylaxis, treatment duration and persisting symptoms.

- Value of prophylaxis in particular situations in highly endemic regions
- Treatment durations in EM patients
- Referred to Lyme NB study comparing treatment length (talk later in conference)
- Resolution of subjective symptoms – his published work and referred to Lyme Prospect (The Netherlands)
- More data is needed to understand ongoing symptoms
- Autoimmune events/coinfection/increased sensitivity to infection/more severe infection could be potential reasons
- Wishlist for PTLDS: biomarkers/pathogenesis/treatments

Sergio Hernández has looked at immune markers in Lyme NB (matched serum and cerebrospinal fluid)

- distinct immune signatures shown in a heatmap
- Immune response role in pathogenesis
- Bannworth's syndrome may be associated with a gene polymorphism (TLR1 gene)

Daša Stupica introduced a 7 day vs 14 day treatment regime for EM with Doxycycline

- 7 days non-inferior to 14 days
- Unfavourable response rare
- 12 month non-specific symptoms and SF-36 showed no difference between patient groups and controls
- Not blinded (may influence symptom reporting)
- Single EM and likely to be region/genospecies specific findings (eg genospecies may disseminate more readily)
- Ongoing study for disseminated disease with multiple EM

Monday 5th September

'Young and Wild': Early career researchers presentations –

Introduced by Allen Steere and Frank Strle

Only the highlighted talk was discussed

- Constantin Takacs (Stanford University USA). 'Chromosome segregation in polyploid *Borrelia burgdorferi* spirochetes is orchestrated by a novel centromere binding-protein, ParZ

Basic science with future translational possibility: clinical relevance to bacterial load /pathogenicity and response to treatment

- **Alice Raffetin (Ch Villeneuve-saint georges, France) 'Multidisciplinary management of suspected Lyme Borreliosis: clinical features of 569 patients and factors associated with recovery at 12 months, a prospective cohort study'**

- Johanna Strobl (Medical University of Vienna, Austria) 'Changes in the human skin immune landscape facilitate tick-borne pathogen transmission'

*Ex-vivo skin model (skin sections from cosmetic surgery!): differences in skin immune response between *Bb s.s.* and *B afzelii*: future use to help prevention/treatment strategies*

Focus for this session is on **Alice Raffetin's** presentation:

- France has 5 Tick-Borne Referral Centres
- Prospective cohort study: Paris and Northern region (569 patients)
- Final diagnosis of confirmed/possible/PTLDS, sequelae/other diagnosis
- Multidisciplinary management with treatment to all patient groups
- Outcomes evaluated at 12 months (recovery/partial recovery/stagnation/deterioration)
- Inappropriate prescription of long-term AB/non-recommended AB/delay from first symptoms to consultation at TBRC/multiple diagnoses prior to referral negatively associated with outcome
- Early management of suspected LD associated with better outcome

Tuesday September 6th

Session: Pathogenesis:

Introduced by Linden Hu (Keynote speaker from Sunday)

Only the highlighted talk was discussed

- **Klemen Strle (Invited speaker, Wadsworth Centre, USA)**
'Understanding mechanisms underlying acute Lyme disease and chronic symptoms'
- Brandon Jutras (Virginia Tech, USA) 'The biology and pathogenesis of the *Borrelia burgdorferi* cell wall'
Structurally unique peptidoglycan – implicated in immunological response?
- Diego Barriaes (CIC bioGUNE, Spain) 'Diet-derived compounds modulate the innate immune response to *Borrelia burgdorferi*'
- Edouard Vannier (Tufts Medical Centre, USA) 'Characterization of the protective antibody response in babesiosis by use of whole pathogen proteome array and a mouse model of cd4 deficiency'

Klemen Strle

- Focus on understanding heterogeneity of symptoms and duration of LB
- PTLDS potential causes: Autoimmunity/metabolism/remaining borrelia antigens/microbiome/persistent infection
- Hernández (previous talk)/Aucott/Strle (EM) longitudinal studies suggest immune response
- Immune response (pathogenic role of IFN α) in post-Lyme symptoms
- Treatment approaches: Target immune response after antibiotic treatment

Tuesday September 6th

Session: Ecology

(introduced by Jean Tsao, Michigan State University, USA)

- Maarten Voordouw (Invited speaker, University of Saskatchewan, Canada) 'Abundance in the host and tick is critical for the transmission success of *Borrelia burgdorferi sensu lato*'
- Valentina Tagliapietra (Fonazione Edmund Mach, Italy) 'Are generalist species replacing specialists?- Implications of hosts species distribution on tick-borne disease along an altitudinal gradient in the Italian Alps'
- Maria Diuk-Wasser (Columbia University, USA) 'The rise of urban tick-borne diseases: the roles of greenspace connectivity and wildlife community assembly'
- Scott Williams (The Connecticut Agricultural Experiment Station, USA) ' Oral delivery of a Modern-Day Systematic Acaricide formulation for pathogen vector management on White-Tailed Deer in Connecticut, USA'

Tuesday September 6th

Poster pitches: second session of 3 minute presentations

- Lyme borreliosis in the Netherlands – Seroprevalence and risk factors
Dieneke Hoeve-bakker, Netherlands (RIVM)
- The Cdkn2a gene product p19 alternative reading frame (p19ARF) is a critical regulator of IFN-mediated Lyme arthritis
Janis Weis, United States (University Of Utah)
- Peripheral blood transcriptional signature of Lyme arthritis in children
Lise Nigrovic, United States (Boston Children's Hospital)
- Pathogen abundance and transmission: *Borrelia burgdorferi* strains that establish high abundance in host tissues have higher transmission success to feeding *Ixodes scapularis* ticks
Christopher Zinck, Canada (University Of Saskatchewan, Western College Of Veterinary Medicine)
- Determining effects of winter weather conditions on nymphal *Ixodes scapularis* and adult *Amblyomma americanum* survival in Connecticut and Maine, USA
Megan Linske, United States (The Connecticut Agricultural Experiment Station)
- Secretoglobin family 1D member 2 (SCGB1D2) protein inhibits growth of *Borrelia burgdorferi* and affects susceptibility to Lyme disease
Michal Tal, United States (MIT)

Tuesday September 6th Session: Tick Biology
Introduction by Olaf Kahl (Tick-radar GmbH, Germany)

- Utpal Pal (Invited speaker, University of Maryland, USA) 'Intricate tick-host pathogen interactions in Lyme disease'
- Jason Huntley (University of Toledo, USA) 'Francisella tularensis exhibits distinct infection and replication kinetics in *Amblyomma americanum* and *Dermacentor variabilis* ticks'
- Boris Klempa (Biomedical Research Centra, Slovakia) 'Experimental tick infections and comparative in vivo transmission studies confirm the vector competency of *Dermacentor reticulatus* ticks for TBE virus'

Tuesday September 6th
Session: 'Lyme in the Lyme light'
Chaired by Hein Sprong and Joppe Hovius (The Netherlands)

This session is dedicated to topics that are controversial and have been the topic of debate.

- Anne Marit Solheim (Sørlandet Hospital, Norway) 'Antibiotic treatment length and clinical features in Lyme Neuroborreliosis'
- Freek van de Schoor and Ewoud Baarsma 'Diagnostic parameters of cellular tests for Lyme borreliosis in Europe (VICTORY study): a case-control study'
- Monica Embers (Invited speaker, Tulane University, USA) 'Chronic *Burgdorferi* infection, lessons from animal models?'

Anne Marit Solheim introduced her RCT that had been referenced by Gary Wormser the previous day

- 2 vs 6 weeks of Doxycycline randomised placebo-controlled double blinded
- Non-inferiority design and conclusion that they could not claim non-inferiority
- Limited by use of a non-validated composite clinical score
- Inclusion of likely less severe cases and few patients with CNS involvement

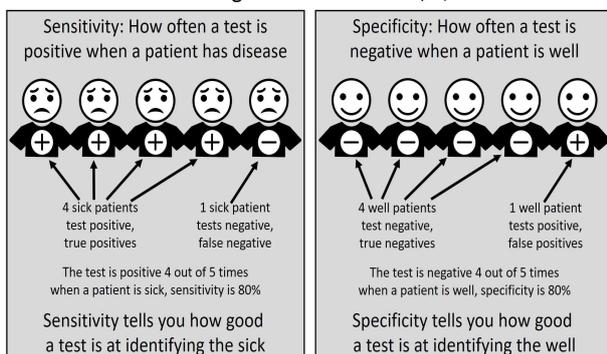
Freek van de Schoor and Ewoud Baarsma: Victory study
(DOI:[https://doi.org/10.1016/S1473-3099\(22\)00205-5](https://doi.org/10.1016/S1473-3099(22)00205-5))

Cellular testing currently is not recommended for Lyme disease testing and this study looked at the diagnostic parameters using a case-control design.

- EliSpot/LTT-MELISA/Spirofind identified along with patient working group
- Compared with control C6-ELISA and standard two-tier testing
- Limited by absence of gold standard and inclusion of mostly EM participants (serological reactivity is low).
- Change of setting for cellular testing
- All 3 cellular tests showed low specificity compared to serological tests (next slide)
- Sensitivities of cellular assays and difficulties of standardisation

Diagnostic Tests: What do sensitivity and specificity mean?

Basic Diagnostic Test Metrics, 2/4



Basic Diagnostic Test Metrics, 4/4

Summary

Sensitivity:

If a test is 80% sensitive, 80% of sick people will test positive.

Specificity:

If a test is 80% specific, 80% of healthy people will test negative.

PPV:

A PPV of 80% means 80% of people who test positive will be sick.

NPV:

A NPV of 80% means 80% of people who test negative will be healthy.

Case courtesy of Stefan Tigges, [Radiopaedia.org](https://radiopaedia.org), rID: 94132

<https://doi.org/10.53347/rID-94132>

Monica Embers presented her work on Lyme disease animal models and autopsy case study.

- Non-human primate model to represent similarities to human infection (eg size/relative bacterial burden)
 - Produces similar symptoms: EM/carditis/arthritis/LNB (CNS/PNS)
 - EM in 1 in 10 animals – others diffuse erythema: skin biopsy PCR +ve in 8/10 animals
 - Xenodiagnosis: ticks infected (detected using IFA) from treated and untreated animals
 - Autopsy brain tissue samples Bb+ve (IFA) after previous diagnosis and treated Lyme disease, with further treatment for late LD
- doi: 10.3389/fneur.2021.628045

Wednesday September 7th

Session: Diagnostics

Introduced by Benoit Jaulhac (University of Strassbourg, France)

- **Volker Fingerle (Invited speaker, Germany) 'Diagnosis of Lyme disease and other TBD's: Limitations of current tests'**
- **Abhijeet Nayak (Amsterdam UMC) 'Development of a new diagnostic test for LB based on antigens discovered by screening a whole proteome microarray'**
- **Ivar Tjernberg (Sweden) 'A novel laboratory approach to discriminate active LB from non-Lyme individuals in addition to anti-Borrelia serostatus'**
- **Olga Stukolova (Russian Federation) 'Development and validation of a protein array for LB diagnostics'**

Diagnostic session with previous talks identifying what we need in our TBD diagnostic wishlist:

Volker Fingerle started with this slide which sums our needs up nicely!



Picture courtesy of

<https://www.healthline.com/health-news/medical-device-used-in-star-trek-is-now-a-reality>

- Issues with direct detection in Lyme disease
- Improvements to serology and the most important diagnostic test
- False positives due to cross reactivity
- Potential of CXCL13 for Lyme NB, but more data is needed

Following talks included current research developing diagnostics for Lyme disease

- Isolation of murine and human antigens to develop a new diagnostic test (The Netherlands)

Russian Federation:

- Use of biomarkers to identify active disease vs previous infection (Sweden)
- Protein array: combination of proteins with an algorithm. Testing in confirmed LD patients and control groups (healthy/non-endemic/cross-reactive and other ID groups).
- Better sensitivity in disseminated disease (92 vs 62%).
- Variable specificity (86-94%).
- Further work on adding new antigens to the algorithm and discovering novel antigens

Wednesday September 7th

Session: Preventative measures against tick-borne diseases -
Introduced by Lars Eisen (CDC, USA)

- **Erol Fikrig (Invited speaker, Yale University, USA) presented 'mRNA vaccination induces tick resistance and prevents transmission of the Lyme disease agent'**

Interesting alternative vaccination design – alerting individual to a tick bite through inflammatory response. Also reduction in ticks ability to feed successfully!

- **Gebbiena Bron (University of Wisconsin, USA) ' A smartphone app to better understand human behaviour and tick encounters – The Tick App, an evolving tool'**

Nice bit of citizen science! Prevention strategies and reporting app. Feedback to user on tick species.

- **Nicole Bézy (Valneva, Austria) 'Development of a multivalent LB vaccine candidate: Results from a phase 2 safety and immunogenicity study in an adult and paediatric study population'**

Pfizer/Valneva vaccine update – phase 3 has started in highly endemic regions of the USA.

Next ICLB 2025 location revealed.....



So...how was it for me?!

- Amazing seeing lots of people together after 2 years of virtual meetings!
- Moved my research forward and strengthened collaborations
- Distributed the LYME-COS leaflets and QR code, so hopefully got some international reach!
- Meeting and connecting with other researchers from USA and Europe
- Talks covering the whole research area of TBD's and the importance of linking Ecology and Tick Biology through to our understanding of LB and other TBD's
- Names to faces for the movers and shakers in LB research!
- Underlining the importance of biobanking for diagnostic development
- Tiring!! I slept very well when I got home!

Thank you to all at LDA
and to Stella and Sandra for all
their support.





Any questions?....